REMARKS

Status of Claims and Amendment

Upon entry of the amendment, which is respectfully requested, claims 27, 28 and 29 will be amended. Claims 18-35 are all the claims pending in the application and are rejected.

Claims 27, 28 and 29 have been amended to remove the recitation of "are specific for said breast cancer."

Information Disclosure Statement

Applicants thank the Examiner for acknowledging the Information Disclosure Statement filed May 8, 2008, by returning a signed and initialed copy of the PTO Form SB/08 A & B form submitted therewith. However, Applicants note that two patent publications were not initialed on the PTO Form SB/08 that accompanied the IDS filed on September 21, 2007. Accordingly, Applicants respectfully request that the Examiner consider these references and return another copy of the PTO Form SB/08 indicating the same.

Response to Rejections Under 35 U.S.C. § 112

1. Indefiniteness

At page 2 of the Office Action, claims 27-35 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

The Office Action asserts that step (b) of claim 27 recites isolating ten or more mRNA or cDNA species specific for "said breast cancer" of step (a) from humans known to have breast cancer and making a comparison of the individuals having breast cancer with those having early stage breast cancer. However, the Office Action appears to assert that there is no

nexus between what is intended in claim 27 and the reference to claim 18. That is, the Office Action asserts that claim 18 makes a comparison between individuals with very early stage breast cancer and normal humans, while claim 27 makes a comparison between two types of breast cancer. The Office Action asserts that claim 28 is similarly problematic.

Further, the Office Action asserts that claim 29 includes a similar step of isolating 10 or more mRNA or cDNA which are specific for said breast cancer according to the method of claim 18. The Office Action asserts that claim 29 is unclear for the same reasons, *i.e.*, claim 18 is concerned with making comparisons between individuals having early stage breast cancer and normal humans while the preamble and language of claim 29 refer to diagnosing "breast cancer" generically. The Office Action requests clarification of the above-discussed matters.

In response, Applicants note that one of ordinary skill in the art would understand from reading the specification, for instance, at page 11, last full paragraph to page 12, 1st full paragraph and page 15, 1st full paragraph to page 16, line 16, that claim 18 is directed to isolating mRNA or cDNA species that exhibit differential expression in normal versus diseased samples. Once identified, the mRNA or cDNA species may be used as "informative" probes that reflect genes which have altered expression in the diseases, or conditions in question, or particular disease stages. Accordingly, claim 18 recites a method of obtaining "informative" probes useful for diagnosing or identifying very early stage breast cancer. Furthermore, step (b) of amended claims 27 and 28 now recites, "isolating 10 or more mRNA or cDNA species which are specific for said breast cancer and are present at different levels in a blood sample from more than one normal human, than in corresponding cells in a blood sample from more than one human who are known to have early stage breast cancer

according to the method of claim 18." Even though the comparison set forth in section (b) of Claims 27 and 28 is between individuals having breast cancer and individuals having very early stage breast cancer, the method of claim 18 is included to describe the "informative" probes. Similarly, claim 29 includes a step of isolating 10 or more mRNA or cDNA species which are specific for breast cancer according to the method of claim 18, and also states, "...wherein the mRNA or cDNA species identified in step (b) are present at a different level in cells in a blood sample from more than one normal human than in corresponding cells in a blood sample from more than one human who are known to have very early stage breast cancer."

Accordingly, the claims prior to the present amendment clearly reflect what Applicants consider to be the claimed invention. However, solely to advance prosecution of the present application, the following claims 27 part (b), 28 part (b) and 29 part (b) have been amended to delete the recitation "are specific for said breast cancer".

Reconsideration and withdrawal of the rejection under § 112, second paragraph, is respectfully requested.

2. Written Description

At page 8 of the Office Action, the rejection of claims 27-35 is maintained under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement, for reasons of record.

Specifically, the Office Action asserts that claims 27-29 set forth a method for obtaining mRNA or cDNA molecules, but the claims do not describe the structure of these molecules. Thus, the Office Action asserts that while one of ordinary skill in the art would conclude that Applicants are in possession of the claimed method for identifying compounds that are differentially expressed using the method set forth in claim 18, one of ordinary skill in the art

would not conclude that Applicants were in possession of the molecules that are differentially expressed themselves, or by extension, methods for using those molecules at the time of filing. Accordingly, the Office Action asserts that the specification fails to meet the written description requirement.

Applicants note that claim 18 is not rejected and point out that in performing the invention, the skilled artisan has no additional need, relative to claim 18, to be taught any correlation between the functional properties of the probes and their structure. Their properties are inherent by virtue of their isolation method. Their method of isolation replaces the need to describe their structure. Thus, Applicants respectfully submit that the specification fully teaches how to identify probes that are useful according to the invention and their use in preparing hybridization patterns for diagnosis. Briefly, claims 27-29 refer to methods and each of these methods is fully described with regard to how that method should be carried out. As such there should be no need to describe the intermediate products which are obtained during performance of that method, or the final product that is obtained from a process claim.

Reconsideration and withdrawal of the rejection under § 112, first paragraph, is respectfully requested.

Response to Rejections Under 35 U.S.C. § 103 (a)

1. At page 4 of the Office Action, the rejection of claims 18 and 20-25 is maintained under 35 U.S.C. § 103(a) as being unpatentable over Ralph *et al.* (U.S. Patent No. 6,190,857) in view of Lukas *et al.* (Journal of Investigative Medicine, Vol. 45, No. 1, page 132A (1997)).

The Office Action asserts that Ralph teaches i) a method for cancer detection and diagnosis that relies upon detecting a response of circulating leukocytes to the disease state, ii)

that the described method may be used to discover disease markers for any disease state that affects the peripheral blood leukocytes, including but not limited to organ defined cancer, and iii) a method which includes steps of providing human peripheral blood mRNAs from both healthy and diseased individuals, amplifying the mRNAs to provide nucleic acid amplification products, separating the nucleic acid amplification products, and selecting those mRNAs that are differentially expressed between normal individuals and individuals having a disease state. Further, the Office Action asserts that the practice of any of these methods would first require that the differentially expressed markers had been isolated, as required in instant claim 18.

The Office Action notes that Ralph does not teach a method wherein the organ defined cancer is very early stage breast cancer, and do not exemplify a method wherein at least ten differently expressed markers are isolated, nor do they exemplify a method wherein between 50 and 100 or between 10 and 500 are selected.

However, the Office Action cites Lukas as teaching differential display analysis in order to identify genes that are differentially expressed in breast ductal carcinoma in situ (DCIS) relative to invasive breast carcinoma, and of identifying 119 mRNA species that were differentially expressed in DCIS. Hence, the Office Action concludes that it would have been *prima facie* obvious to modify the methods of Ralph so as to apply such to the study and diagnosis of DCIS, following the guidance of Lukas to achieve the present invention.

Applicants previously pointed out that one of ordinary skill in the art would not reasonably combine the teachings of Ralph and Lukas because Lukas is entirely silent as to whether blood cells in a patient with DCIS would exhibit modified expression. However, the Office Action asserts that this argument is not persuasive, because this is a piecemeal analysis

as it is Ralph who provides the clear teaching to look to blood as a source of markers for cancer.

Applicants further pointed out that Lukas only disclose results from a single patient; however the Office Action finds this argument irrelevant. The Office Action argues that Ralph provides clear guidance as to how to practice their method, and Lukas is relied upon merely for the suggestion that one of skill in the art would have thought to look for markers, or differentially expressed genes for very early stage breast cancer.

Applicants reiterate their position that Ralph compares gene expression levels in blood samples from patients with metastatic prostate or breast cancer. The Office Action argues that while these are the exemplified embodiments in Ralph, the reference must be considered for all it teaches. According to the Office Action, Ralph expresses in their teaching that their methods could apply to organ defined cancers.

Initially, pursuant to M.P.E.P. 2143.02, "[e]vidence showing there is no reasonable expectation of success may support a conclusion of nonobviousness."

As previously argued, the method of Ralph is concerned with a comparison of gene expression levels in blood samples from patients with metastatic cancer which involves direct contact of blood cells with metastatic diseased cells. Such direct contact of blood cells with diseased cells is required by Ralph to elicit an immune response that is detectable in the peripheral blood mononuclear cells (PBMCs). In contrast, Applicants' claimed method is directed to a noninvasive technique for cancer diagnosis in which tumor cells are not directly examined. Instead, because very early stage breast cancer is confined to breast tissue, i.e., milk

ducts, there is no direct contact of the tissue with the blood so that non-tumor cells are isolated from blood and examined for altered gene expression by the claimed method.[2]

Further, there is no teaching or suggestion by Ralph to obtain probes from breast cancer patients using blood not in direct contact with cancer cells, or to prepare a gene transcript pattern for the diagnosis of cancers using such probes, as presently claimed. In fact, Ralph teaches generating probes from blood samples of patients with metastatic cancer. Additionally, as acknowledged by the Office Action, Ralph does not teach a method in which the cancer is very early stage breast cancer (see page 6, 3rd full paragraph of Office Action mailed February 8, 2008). Thus, it would not have been obvious to extend the teachings of Ralph to all organ defined cancers such as very early stage breast cancer.

Lukas does not cure the deficiencies of Ralph because Lukas is cited by the Office Action merely for the asserted suggestion that one of skill in the art would have thought to look for markers, or differentially expressed genes for very early stage breast cancer. As previously argued, Lukas is a deficient reference because Lukas is silent as to whether blood cells in a patient with breast ductal carcinoma would have modified expression, or that such modified expression has diagnostic value. In fact, Lukas adds nothing further to the disclosure of Ralph because, at most, Lukas teaches that tumor cells exhibit altered expression.

Thus, based upon the teachings of Ralph, which requires direct contact between blood and cancer cells to elicit detectable changes, one of ordinary skill in the art would not have

[2] As previously presented, there are fundamental differences between metastatic and non-metastatic cancers so that metastatic breast cancer cannot be equated to non-metastatic, very early stage breast cancer.

expected to successfully diagnose very early stage breast cancer with the presently claimed method which is based upon obtaining a display of altered gene expression from blood where no direct contact between the blood cells and disease cells is involved. Accordingly, because neither Ralph nor Lukas teaches or suggests that very early stage breast cancer may be detected or diagnosed using non-tumor cells, one of ordinary skill in the art would not have been motivated, or have had a reasonable expectation of success to make such a combination.

Applicants note that the Declaration by Dr. James Mackay (a leading oncologist in London)[3] supports this argument. The premise of the Declaration is that although Ralph refers to organ defined cancers, in view of the knowledge in the art regarding prostate cancer, one of ordinary skill in the art understood that Ralph may only be applicable to certain types of organ defined cancers. Namely, those which exhibit metastatic potential, or are metastatic and have either circulating cancer cells in the peripheral blood (metastatic) or debris or cellular components from those cells or from cells with metastatic potential. As discussed in the Declaration by Dr. Mackay, the method of Ralph relies on cancer cells or their debris or cellular components coming into direct contact with peripheral blood cells in order to elicit an immune response that is detectable in those blood cells. In prostate cancer, the point at which metastatic potential can be reached is relatively early compared to breast cancer and would occur while the cancer was still confined to the organ, namely the prostate gland. Evidence that some organ confined prostate cancers are metastatic is shown in the Declaration.

In contrast, metastatic potential in breast cancer is reached at a much later stage and earlier stages of breast cancer would not be expected to have metastatic potential or become

[3] The Declaration to be provided in a supplemental submission.

metastatic. In particular, very early stage breast cancer would not exhibit any metastatic potential, and thus no cancer cells or their debris or cell components would be released into the blood system. As such very early stage breast cancer cells or parts of these cells would be unable to achieve direct contact with peripheral blood cells, alterations affecting their gene expression would not be expected by one of ordinary skill in the art to be detectable.

In view of the above reasons, one of ordinary skill in the art would have interpreted the teachings in Ralph to be directed to organ defined cancers in which cancer cells or their debris or cellular components were released into the peripheral blood system. While this would encompass many organ confined prostate cancers and a limited number of organ defined breast cancers, it would certainly not extend to very early stage breast cancer where cells have not yet reached metastatic potential. Thus, one of ordinary skill in the art would not have been motivated to combine Ralph and Lukas to extend the teaching of Ralph to encompass very early stage breast cancer, nor would one of ordinary skill in the art have had a reasonable expectation of success of detecting altered gene expression for very early breast cancer based upon the disclosure of Ralph or Lukas. The method of Ralph is clearly based on direct contact of blood cells with disease (tumor) cells, and such teachings would be in line with the knowledge available to one of ordinary skill in the art at the time the invention was made regarding the nature of prostate cancer. One of the ordinary skill in the art would not have been inclined or motivated to extend the teachings of Ralph beyond what was credible, *i.e.* would not extend it to very early stage breast cancer.

Thus, Applicants respectfully submit that the present invention as claimed, is not obvious relative to the disclosure of Ralph. Whereas Ralph relies on direct contact between cells or their debris or cellular components (and explicitly states so) the present method does not rely on such

direct contact and this has been proved by analysis of samples from DCIS and LCIS patients (in which the disease is localized and has not even extended beyond the milk ducts) in which gene expression alteration in distant peripheral blood cells has been observed (See Declaration filed September 27, 2007). Applicants point out that this is a novel and surprising effect not disclosed by Ralph and that Lukas does not alter this conclusion. In line with the knowledge in the art at the time, tissue samples were analyzed and Lukas does not teach about systemic effects which would occur distant to the site of the disease where no direct contact between disease cells (or their components or debris) and peripheral blood cells would have occurred. The present invention thus provides, for the first time, a diagnostic method for very early stage breast cancer using a blood sample.

Reconsideration and withdrawal of the rejection under § 103(a) is respectfully requested.

2. At page 6 of the Office Action, the rejection of claims 19, 26, 27, 28, 29, 30, 31, 32, 33, 34, and 35 is maintained under 35 U.S.C. § 103(a) as being unpatentable over Ralph *et al.* in view of Lukas *et al.* as applied to claims above, and further in view of Wadhwa *et al.* (Molecular Biotechnology, Volume 6, pages 213-217).

The Office Action acknowledges that neither Ralph nor Lukas disclose a method wherein identified isolated nucleic acid markers are prepared on a solid support, namely a filter. The Office Action asserts that Wadhwa disclose a reverse Northern assay of DNA fragments isolated from differential display, and that this method has advantages over traditional Northern blots wherein the differentially displayed molecules were PCR amplified, bound to a membrane filter, and cDNA probes prepared from total RNA from cells. Hence, the Office Action concludes that

it would have been obvious to substitute the Northern assays taught by Ralph in view of Lukas with the reverse Northern assays as taught by Wadhwa to achieve the present invention.

Wadhwa does not cure the deficiencies of Ralph or Lukas in view of the reasons set forth above and previous by presented (see Amendment filed May 8, 2008). Further, because Wadhwa is merely relied upon by the Office Action for teaching a technical assay, i.e., reverse Northern assay of DNA fragments isolated from differential display, the addition of Wadhwa does nothing further to render the claimed invention obvious to one of ordinary skill in the art.

Reconsideration and withdrawal of the rejection under § 103(a) is respectfully requested.

Response to Obviousness-Type Double Patenting Rejections

At page 10 of the Office Action, claims 18-35 are *provisionally* rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-36 of copending U.S. Application No. 11/149370 for reasons of record.

As this is a provisional rejection, Applicants respectfully request that the rejection be held at abeyance until an indication of allowable subject matter.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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